Intestinal perforation after pediatric liver transplantation: risk factors and management

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ABSTRACT

Background. Intestinal perforation (IP) after pediatric liver transplant (PLT) is an uncommon complication with high mortality reported. The aim of this study is to identify the risk factors and management of this complication.

Material and methods. Retrospective study of IP after PLT from January 2014 to October 2020.

Results. Four intestinal perforations were indentificated in 102 PLT (3,9%). Three patients with BA and one neonate with hemochromatosis (HC) presented this complication. The mean weight of patients with IP was 6.3± 2.5kg (3.1-9) and 19.9 ± 15.4kg for the rest (p<0,05). All IP with BA had a previous laparotomy. Two living donors and two left lateral reduced liver were implanted. The diagnosis of intestinal perforation was done on day 11 ± 3.3 (8-15 days). Diagnosis was suspected with clinical and biological signs of perforation, CT scan confirmed the diagnosis in patiens with BA and by direct visualization through the mesh for temporary closure in the patient with hemocromatosis. Urgent laparotomy was performed. We identified three colonic perforations, all of them in BA patients and all repaired with direct suture. The patient with HC presented multiple perforations secondary to necrotizing enterocolitis requiring an ileostomy and finally died due to multiorgan failure.

Conclusion. Intestinal perforation after PLT is an infrequent complication. Age, weight, previous laparotomy and BA could be risk factors for IP in PLT. Urgent laparotomy after diagnosis should be performed in order to reduce mortality. Isolated IP with adequate treatment might not affect long term outcomes after pediatric liver transplantation.

KEY WORDS: Intestinal perforation; Liver transplantation; Pediatric liver transplant.

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PERFORACIÓN INTESTINAL TRAS TRASPLANTE HEPÁTICO PEDIÁTRICO: FACTORES DE RIESGO Y MANEJO

RESUMEN

Introducción. La perforación intestinal (PI) tras trasplante hepático pediátrico (THP) es una complicación poco frecuente, pero con una elevada mortalidad. El objetivo de este estudio es identificar los factores de riesgo y el manejo de esta complicación.

Material y métodos. Estudio retrospectivo de la PI tras THP entre enero de 2014 y octubre de 2020.

Resultados. Se hallaron 4 perforaciones intestinales en 102 THP (3,9%). Presentaron esta complicación 3 pacientes con atresia biliar (AB) y un neonato con hemocromatosis (HC). El peso medio de los pacientes con PI era de 6,3 ± 2,5 kg (3.1-9) y de 19,9 ± 15,4 kg en el caso del resto (p<0,05). Todos los pacientes con PI y AB habían sido sometidos previamente a laparotomía. Se implantaron 2 hígados de donantes vivos y 2 hígados laterales reducidos izquierdos. El diagnóstico de perforación intestinal se efectúo en el día 11 ± 3,3 (8-15 días), sospechándose con signos clínicos y biológicos de perforación, y confirmándose mediante escáner en los pacientes con AB y mediante visualización directa a través de la malla para el cierre temporal en el paciente con hemocromatosis. Se llevó a cabo laparotomía de urgencia. Se identificaron 3 perforaciones de colon, todas ellas en pacientes con AB y reparadas con sutura directa. El paciente con HC presentaba múltiples perforaciones secundarias a enterocolitis necrotizante que precisaron ileostomía, falleciendo finalmente como consecuencia de un fallo multiorgánico.

Conclusión. La perforación intestinal tras THP es una complicación poco frecuente. La edad, el peso, las laparotomías previas y la AB podrían ser factores de riesgo de PI en el THP. Para reducir la mortalidad, es conveniente practicar una laparotomía de urgencia tras el diagnóstico. Una PI aislada con un adecuado tratamiento puede no influir en los resultados a largo plazo tras un trasplante hepático pediátrico.

PALABRAS CLAVE: Perforación intestinal; Trasplante hepático; Trasplante hepático pediátrico.

INTRODUCTION

The underlying cause of intestinal perforations (IP) in transplanted patients remains unclear and still subject

Table 1. Demographic and clinical data of the patients with perforations

Patients	*Age*	*Sex*	*Weight (kg)*	*PD*	*PL*	*DDIP*	*IPL*
1	6 months	Female	5,8	BA	Yes	10	TC
2	12 months	Female	9	BA	Yes	8	TC
3	15 days	Male	3,1	HC	No	14	Yeyunal +Roux-Y
4	8 months	Male	7,2	BA	Yes	15	TC

PD, primary disease; BA, biliary atresia; HC, hemocromatose; PL, previous laparotomy; DDIP, Date of diagnosis of intestinal perforation; IPL, localization of intestinal perforation; TC, transverse colon.

of research given the impact on the prognosis. Some risk factors have been identified such as biliary atresia (BA) as a primary disease, previous laparotomy, prolonged time of surgery, young age, low weight, longue portal clamping time, subsequent laparotomy, portal vein thrombosis, treatment with high-dose steroids, open abdomen and cytomegalovirus (CMV) infection[1]. The prognosis in the immediate postoperative period of a liver transplant can be worsened by biliary, vascular and gastrointestinal perforation. IP is reported in 1-2% of adults and around 6.4% to 20% in the pediatric population with a mortality rate of 30% to 50%[2,3].

The aim of this study was to describe the incidence of IP in infants after pediatric liver transplant (PLT) experienced at our department and analyze the associated risk factors and management.

MATERIAL AND METHODS

From January 2014 to October 2020, all PLT (recipient <16 years old) performed in our institution were retrospectively reviewed. Four patients (3.9%) of 102 PLT were diagnosed with IP.

Patient were divided into two groups based on intestinal perforation after PLT, the following parameters were analyzed and compared between groups: age, sex, underlying liver disease, previous surgery, liver graft type, time of warm isquemia as orientative of portal clamping time, interval between PLT and diagnosis of IP, perforation site, type of surgery and mortality.

Stata 13.1 was used (StataCorp, College Station, TX). For continuous data, variables are expressed as mean (standard deviation). Categorical data is shown as number and percentage. Student´s t test was used (continuous data normally distributed) and Mann-Whitney U test (non-normally distributed variables). Pearson Chi-Square or Fisher's exact test was used for categorical variables. A multivariable analysis was not conducted due to the sample size. A p value <0.05 was considered statistically significant.

RESULTS

A total of 102 PLT were performed, 63 (61.9%) females and 49 (48.1%) males. The mean age and weight at the transplantation was 59 months (0.5-201months) and 19.3 ± 15.4kg (3.1-73 kg) respectively. Cholestatic diseases (44.1%) and metabolic disorders (33.3%) were the principal indications for PLT. BA was the most frequent underlying pathology, it was presented in 27 patients (26.5%), followed by propionic acidemia in 10 patients (9.8%).

Four patients were diagnosed with intestinal perforation (3.9%) after PLT (Table 1), three patients with BA and one with neonatal hemochromatosis (HC). None of the patients with IP was older than 12 months (6 ± 4.5 [1-11]) at the moment of the liver transplant. The mean weight of those transplanted with IP was 6.3 ± 2.5 kg vs 19.9 ±15.4 ($p<0.05$). All IP with BA had a previous laparotomy (portoenterostomy procedure). Regarding the type of graft, two of them were living donors and two left lateral reduced liver ($p>0.05$). The diagnosis was made at day 11±3.3 (8-15 days). Patients with BA presented moderate abdominal distension, infection signs with inflammatory parameters in laboratory tests and CT scan showing signs of perforation. Patient with neonatal hemochromatosis was the only one who had a temporary abdominal closure with transparent mesh[4], diagnosis was made by direct vision of the perforations. Despite the fact that all the patients had abdominal drainage, collecting the area of the biliary-enteric anastomosis and posterior to the liver cut surface, in no case was it useful for the diagnosis of intestinal perforation.

Urgent laparotomy was performed in all patients. Localization of intestinal perforations in patients with BA was transverse colon, all of them were punctiforms, on the antimesenteric edge and affecting less than a quarter of intestinal circumference. After revitalizing the edges, primary suture was performed in all of them, avoiding ostomies.

There were no episodes of re-perforation or complications after that. One patient had an active infection of CMV at the time of perforation. Risk factors for IP are summarized in Table 2.

Table 2. Risk factors.

	IP (N°4)	*no IP (N° 98)*	*p*
Sex (male/female)	2/2	61/38	NS
Age (months)	6 ± 4,5	64.7 ± 57.9	<0.05
Weight (kg)	6.3 ± 2.5	19.9 ± 15.4	<0.05
BA	3 (75%)	24 (24.5%)	<0.05
Laparotomy	3 (75%)	26 (26.5%)	<0,05
Warm isquemia (min)	38 ± 9	37 ± 11	NS
Colangitis	1 (25%)	17 (17.3%)	NS
CMV infection	1 (25%)	13 (13.3%)	NS
Graft rejection	0	7 (7.1%)	NS

IP, intestinal perforation; CMV, cytomegalovirus.

One patient had one cholangitis episode and none of them presented graft rejection in the short term follow-up. Patients with HC presented multiple perforations secondary to necrotizing enterocolitis requiring resection and ileostomy. This patient also presented portal thrombosis and finally died on day 24 after LT (46 days of life) due to multi-organ failure.

DISCUSSION

Gastrointestinal perforation has been reported with an incidence of 6.4%-20% with a mortality as high as 30% to 50% and 30% to 78% following reperforation[1,3]. The results of this study suggest that IP prognosis does not have to be worse if it is detected rapidly and treated properly since the type of perforation and outcome of patient with enterocolitis could be considered as a different entity. Previous reports of bowel perforation after PLT are summarized in Table 3[1,2,5,6]. Sepsis development is due to late diagnosis and is the main responsible of mortality. The inespecificity of the clinical manifestations makes diagnosis challenging and, consequently, a late treatment. Patients with IP usually present a mild abdominal distention and elevation of serum inflammatory markers. Abdominal CT was the most useful tool that revealed the presence of pneumoperitoneum and confirmed the suspicions in the postoperative period of liver transplantation. Abdominal drainage characteristics may help to the diagnosis[7], in none of our patients the drain had pathological products, perhaps because we left only one drain in the posterior area. We are not planning to change this attitude, first of all due to the infrequency of this complication and the fact that in most patients we remove the drains prior to the mean days of diagnosis of the perforation. In one patient the diagnosis was made with direct vision through the mesh.

Sanada et al. with a median time at the diagnosis of 10.8 days and an incidence of 2.5% of IP in 148 patients[5]. The diagnosis of intestinal perforation was made around the tenth day after transplantation in the published series; our results do not differ from those obtained in the rest of the studies.

Since the incidence of IP is ten times more often in pediatric transplant patients compared to adults, it is easy to assume that lower weight and young age are risk factors[8]. Aslan et al. reports mean age of patients with IP was significantly lower than those without IP (P<0.05),

Table 3. Reports of intestinal perforation after pediatric liver transplantation.

Report	*Sample*	*IP (%)*	*DD*	*SP*	*Treatment*	*RF*	*Mortality*
Sanada et al. 2011	148	2.5	11	Ileum: 4 Y- Roux: 1	SC: 4 Ostomy: 1	Long duration of transplant surgery	50%
Yanagi et al. 2016	69	15.9	9	Jejunum:2 Y-Roux: 2 Ileum: 5 T-Colon:2 Other site: 2	SC: 10 Ostomy: 3	Prolonged operative time	0%
Barut et al. 2019	370	10	9-12	Jejunum: 7 Ileum: 17 T-colon: 4 Other site: 7	SC: 20 Ostomy: 17	Perforation site	40,5%
Aslan et al. 2020	131	19	8	Jejunum: 10 Ileum: 5 Other site: 4	SC: 19	Younger, underweight, previous operated, use of mesh	31.57%
Barila et al. 2023	102	3.6	11	T-colon: 3 Y limb: 1	SC: 3 Ostomy: 1	Young age, low weight, previous surgery, BA	25%

DD, date of diagnosis; IP, incidence of perforation; BA, biliary atresia; SP, site of perforation; RF, risk factor of IP; SC, simple closure.

12.57 ± 10.77 months vs 56.78 ± 64.33 months[1], similar results to our study. However, Yanaki et al. report a cohort of 70 patients with 13 IP with an incidence of IP higher in adolescent's patients than in the young children. They concluded that this was probably due to longer hepatectomy and high association of previous laparotomies in the adolescents[6].

The etiology of IP following LT remains obscure and it is considered to be multifactorial. It has been suggested that it might develop, especially, when the primary disease is BA. Besides being the most common indication of transplantation in children, BA is a significant cause of intraabdominal adhesions secondary to the Kasai procedure and recurrent cholangitis that produce inflammatory reactions, which increase the severity of adhesion. Extensive adhesiolysis and the use of thermal dissection with electrocautery may produce serosal injuries that are not diagnosticated during the transplantation. The fact that the bowel perforations in our series were located in the transverse colon could be related to this factor, although diagnosis would have been expected closer to the transplant. In addition, BA is associated with hypoplasia and risk of portal vein thrombosis, which have also been described as risk factors for intestinal perforation.

CMV has also been reported to be a causative factor of GIP after LT. It is postulated that the mechanism is through primary intestinal infection with subsequent ulceration and perforation[9].

It has been argued that long duration (>65 min) of the portal clamp time interferes with the splenic circulation and constitutes a risk factor for IP[10]. In the present study, there was not a significant difference regarding warm ischemic time between the patients with IP and those without. However, the patient with multiple perforation presented a portal thrombosis probably of multifactorial origin.

IP can be anywhere in the gastrointestinal system, most frequent in 40-50% in the ileum, 15-20% jejunum et 10-15% in the colon. However, the most common site in the present cohort was transverse colon. The site of perforation might have a significant impact on the overall survival of patients. Aslan et al. presented an incidence of 14.5% IP, 44% of the IP had perforation at more than one place, however, this fact has not been linked to a worsen prognosis compared to a single IP[1].

It has been suggested that patients with stomas had a significantly higher overall survival than primary suture. Ostomies were performed in 46% of the patients and the survival analysis of the patients with IP concluded that patients with stomas had a significantly higher overall survival in comparison to patients without stomas, although without reaching statistical significance. In the present study, primary anastomosis was performed in 75% of the patients and none of them needed a relaparotomy due to a second episode of perforation. We advocate for primary anastomosis if the intestine allows it in pediatric population, thus avoiding the need of a second surgery in a patient who has already a basal delicate situation and reduces the risk of catheter contamination and sepsis. Mortality rate is known to increase with reperforation, the incidence of reperforations reported is 31-53% [11]. In Barut et al. study the incidence reperforation was 24% with a mortality of 75%. In fact, the multivariate analysis for independent risk factors of mortality showed that only reperforation was an independent risk factor for the mortality of PLT patients[2].

Yanagi et al report no mortality due to early indication of emergency laparotomy once the diagnostic suspicion was established[6]. Our experience support that isolated IP survival is excellent when it is rapidly diagnosed and treated.

In conclusion, IP is a complication after PLT which can seriously worsen the prognosis but with a correct diagnosis and treatment the survival is excellent. Careful dissection and avoiding iatrogenic injury during operation are decisive to avoid this complication. Given the clinical suspicion, we consider necessary to perform a CT scan and an emergency surgical intervention. We believe primary anastomosis is feasible and does not increase the mortality in absence of intestinal isquemia stigmas.

DECLARATIONS OF INTEREST

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